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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/056,908	HINKEL ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-17,19,20,23,25-31 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17, 19-20, 23, 25-31 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/14/05 has been entered. Claim 36 was added in this paper. Claims 13-17, 19-20, 23, 25-31 and 36 are pending and examined herein. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are:

The claim lacks a step to identify how the identity of the single nucleotide polymorphism can occur based on "the identity of said microbead" if the hybridization tag used is not on the allele specific primer. In this case, the hybridization tag would be the same for both alleles since

presumably the reverse primer would be the same for both alleles of a polymorphism. Thus, in order to identify the single nucleotide polymorphism based on the microbead identity, there must be some further means for identifying the allele other than the simple identity of the microbead. Clarification is required..

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 13, 14, 15, 16, 17, 20, 23 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lai *et al.* in view of Fulton *et al.* (Clinical Chemistry, 43(9):1749-1756 (1997)).

Lai *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

(a) providing at least one primer pair, said primer pair containing a reverse primer and a forward primer comprising a 3' end specific for an allele of a single nucleotide polymorphism of interest and a hybridization tag that identifies the primer, said hybridization tag not complementary to the sequence containing said single nucleotide polymorphism of interest (¶ 0179);

(b) combining said at least one primer with a sample containing single-stranded polynucleotides under stringent conditions which allow hybridization of said primers to complementary sequences in said single-stranded polynucleotides (¶ 0179);

(c) extending hybridized primers by primer extension to produce an extension product wherein said extension product comprises said hybridization tag and a detectable label (¶ 0179);

(d) hybridizing said extension products by said hybridization tag or the complement thereof under stringent conditions to capture a probe wherein said capture probe is coupled to a microbead, said microbead identifying said capture probe (¶0181, ¶ 0182);

(e) detecting the hybridization of said extension product to said capture probe by the presence of said detectable label (¶ 0182); and

(f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (¶ 0182).

With regard to claim 14, Lai *et al.* teach that the reverse primer comprises a detectable label (¶ 0179).

With regard to claim 15, Lai *et al.* further teach that the reverse primer is a universal primer that is universal to both alleles being tested (¶ 0185, also figure 12).

With regard to claim 16, Lai *et al.* teach repeating the extension step in subsequent rounds of PCR (¶ 0180).

With regard to claim 17, Lai *et al.* teach that this assay can be multiplexed, thus comprising a plurality of primer pairs specific for a plurality of single nucleotide polymorphisms (¶ 0183).

With regard to claim 20, Lai *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one group of at least 2 primers in each group, wherein each primer comprises a hybridization tag that identifies said primer, and each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest (¶ 0179 and ¶ 0183);

b) combining said at least one group of primers with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primers to complementary sequences in said single-stranded polynucleotides (¶ 0179, inherent in PCR);

c) extending hybridized primers by primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (¶0179-0180);

d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a microbead that identifies said capture probe (¶ 0182);

e) detecting the hybridization of said extension product to said capture probe using said detectable label (¶ 0182);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (¶ 0182).

With regard to claim 23, Lai *et al.* teach a method further comprising a plurality of said primer groups, each primer group specific for a different single nucleotide polymorphism of interest (¶0183).

Claim 36 differs from claim 13 because claim 36 requires that the primer pair comprise a reverse primer comprising a hybridization tag not complementary to the sequence containing said SNP of interest, and a forward primer comprising a 3' end specific for an allele of a single nucleotide polymorphism of interest. Lai et al. teach that "either the first or second primer can be the selective allele-specific primer comprising a 3' end designed to overlap the location of the SNP (¶ 0183)" and that "where the second primer is the selective primer, it must be labeled with a different label than the second primer for the other allele because both alleles with use the same first primer comprising the same unique sequence and thus the second primer extension products from the two alleles will not be distinguishable by their different capture sequences (¶0184)." Thus, Lai et al. specifically teach that a first primer that is allele-specific and a second primer that comprises the tag.

Lai *et al.* do not teach a method wherein the detection is by flow cytometry. (For clarity of the record, it is noted that Lai *et al.* at ¶ 0264 do teach detection by flow cytometry. However, this disclosure is not supported by Lai *et al.*'s provisional application, which support is relied upon in this rejection).

Fulton *et al.* teach methods of sorting and detecting microspheres which utilize flow cytometry, and in particular teach these methods in conjunction with nucleic acid hybridization

methodologies (p. 1753-1755). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Lai *et al.* so as to have included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.*, including any necessary modification of the beads taught by Lai et al. necessary for the practice of the flow cytometry methods taught by Fulton et al. One would have been motivated to utilize such methodology because Fulton *et al.* teach that their system "represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions..." and that their system "...is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis..." offering "excellent sensitivity, precision, speed, and economy (p. 1775)." Thus, one would have been motivated to use the flow cytometry based methods taught by Fulton et al. to detect alleles as taught by Lai *et al.* in order to take advantage of such a system as taught by Fulton *et al.*

7. Claims 19, 25, 26, 27, 28, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lai *et al.* in view of Fulton *et al.*, as applied to claims 13, 14, 15, 16, 17, 20, and 23 in the previous rejection, and further in view of Wallace *et al.* (WO 93/25563).

The teachings of Lai *et al.* in view of Fulton *et al.* are described in the previous rejection.

With regard to claim 19, Lai *et al.* in view of Fulton *et al.* do not teach the application of this methodology for diagnosing a disease, condition, disorder or predisposition. However, at the time the invention was made, it was routine in the prior art to utilize the detection of single nucleotide polymorphisms for the detection of any number of diseases. For example, Wallace *et al.* teach the detection of diseases such as sickle cell anemia or thalassemia caused by a defective

allele (p. 5, first full paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have utilized the methods taught by Lai *et al.* in view of Fulton *et al.* for the detection of disease as suggested by Wallace *et al.* in order to have provided a method for detecting diseases caused by single nucleotide polymorphisms.

With regard to claim 25, Lai *et al.* in view of Fulton *et al.* do not teach methods wherein said primer extension is single base primer extension. Wallace *et al.* teach single primer extension for the detection of alleles, wherein the primer comprises a hybridization tag that identifies the primer (for example, p. 13-14). For example, Wallace *et al.* teach a hybridization based method for the detection of single nucleotide polymorphisms which comprises steps of hybridizing a group of at least two primers which comprise hybridization tags that identify the primers to sample, extending primers and hybridizing the extended primers to a capture probe (p. 9-10; p. 13-14; Figure 4 and 5). The method taught by Wallace *et al.* is a single base extension (see figure 4).

With regard to claim 26, the single base extension is achieved by using only a single type of nucleoside triphosphate, namely all deoxynucleotide triphosphates, and more specifically, to each extension reaction only a single labeled deoxynucleotide triphosphate was added (p. 13-14).

With regard to claims 27 and 28, Wallace *et al.* teach that the primer extension can be accomplished using chain terminating nucleotides, namely dideoxynucleoside triphosphates (p. 10, last line).

With regard to claim 31, Wallace *et al.* teach that their methods include methods for diagnosing diseases such as sickle cell anemia or thalassemia caused by a defective allele (p. 5, first full paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Lai *et al.* in view of Fulton *et al.* in order to have utilized the single nucleotide primer extension method taught by Wallace *et al.* One would have been motivated to utilize the methodology taught by Wallace *et al.* for allele specific detection because Wallace *et al.* specifically teach this as an application of their method and specifically suggest that the capture oligonucleotides of their method be attached to a solid support (p. 5). The combination of the methods of Lai *et al.* in view of Fulton *et al.* and further in view of Wallace *et al.* would have provided an alternative and effective method for the detection of polymorphisms in samples, useful, as taught by Wallace *et al.* for the detection of diseases such as sickle cell anemia. Therefore, in view of the teachings of Lai *et al.* in view of Fulton *et al.* and Wallace *et al.*, the instantly rejected claims are prima facie obvious.

8. Claims 13, 14, 15, 16, 17, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallace *et al.* (US5639611) in view of Gerry *et al.* (J. Molecular Biology, 292:251-262 (1999)) and further in view of Fulton *et al.*

With regard to claim 13, Wallace *et al.* (US) teach a method for detecting a single nucleotide polymorphism comprising:

(a) providing at least one primer pair, said primer pair containing a reverse primer and a forward primer comprising a 3' end specific for an allele of a single nucleotide polymorphism of interest (Col. 2, lines 20-25; Col. 3, lines 50-57);

(b) combining said at least one primer with a sample containing single-stranded polynucleotides under stringent conditions which allow hybridization of said primers to complementary sequences in said single-stranded polynucleotides (Col. 4, lines 1-5);

(c) extending hybridized primers by primer extension to produce an extension product wherein said extension product comprises said hybridization tag and a detectable label (Col. 4, lines 1-5);

Wallace *et al.* (US) further teach the capture of PCR products using a biotin-streptavidin interaction for the detection of a particular allele (Col. 3, lines 20-25).

With regard to claim 14, Wallace *et al.* (US) teach that either the forward or the reverse primer can contain a detectable label (Col. 6, lines 60-65).

With regard to claim 15, Wallace *et al.* (US) further teach that the reverse primer is a universal primer that is universal to both alleles being tested (Col. 3, lines 50-60, the BGP2 primer is used as the reverse primer for both alleles).

With regard to claim 16, Wallace *et al.* (US) teach repeating the extension step in multiple rounds of PCR (Col. 4, lines 5-10).

With regard to claim 19, Wallace *et al.* (US) exemplify the method for the detection of sickle cell anemia alleles, and specifically teach a method for diagnosing sickle cell anemia (Col. 3-4; Claim 3).

Wallace *et al.* (US) do not teach a method wherein the forward primer comprises a hybridization tag that identifies the primer, said hybridization tag not complementary to the sequence containing the single nucleotide polymorphism of interest, nor do they teach hybridizing extension products via the tag to a probe coupled to a particle, detecting the hybridization and identifying the single nucleotide polymorphism based upon the identity of said particle. Wallace *et al.* further do not teach a method wherein the at least one primer pair comprises a plurality of primer pairs specific for a plurality of single nucleotide polymorphisms.

Gerry *et al.* teach a universal DNA microarray method for multiplex detection of point mutations. In the methods taught by Gerry *et al.* allele specific primers are utilized which comprise a 3' end specific for an allele of a single nucleotide polymorphism of interest and a 5' that comprises a hybridization tag that identifies the primer, said hybridization tag no complementary to the sequence containing said single nucleotide polymorphism of interest (Figure 1(a); Table 3). After an allele specific reaction (in this case, ligase detection reaction), the reacted primers are hybridized to a capture probe and detected via a detectable label (p. 260, second column). The location of the detection spot on the array (i.e. the identity of the particle to which the capture probe is coupled) identifies the polymorphism and allele present in the sample (p. 257, Figure 3).

With regard to claim 17, Gerry *et al.* teach a plurality of primers that are specific for a plurality of single nucleotide polymorphisms (p. 260).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Wallace *et al.* so as to have used the binary primer (having an allele specific portion and a hybridization tag) taught by Gerry *et al.* One would have been motivated to have modified the method taught by Wallace *et al.* in order to take advantage of the benefit of the "zip-code" arrays taught by Gerry *et al.*, who teach, "Since the zip-code sequences remain constant, and their complement can be appended to any set of LDR primers, our zip-code arrays are universal. Thus, a single array can be programmed to detect a wide range of genetic mutations...The universal zip-code array approach introduced here has the potential to allow rapid and reliable identification of low abundance mutations in multiple codons of numerous genes (p. 258-259)." Thus, the use of the zip-code methodologies

taught by Gerry *et al.* with the methods of Wallace *et al.* would have afforded one of ordinary skill in the art the opportunity to expand the methods taught by Wallace *et al.* for the detection of multiple mutations and codons.

The teachings of Wallace *et al.* in view of Gerry *et al.* do not teach a method wherein the capture probes are attached to microbeads and wherein the detection occurs by flow cytometry.

Fulton *et al.* teach a method which is very similiar to the method taught by Wallace *et al.* in view of Gerry *et al.* in that it utilizes primers with capture tags which are used to differentiate primers in a sample via hybridization to a tag complement. Fulton *et al.* utilize capture probes attached to microbeads and detection via flow cytometry. Fulton *et al.* teach methods of sorting and detecting microspheres which utilize flow cytometry, and in particular teach these methods in conjunction with nucleic acid hybridization methodologies (p. 1753-1755). Fulton *et al.* teach the multiplexed assays which utilize the microspheres are suitable for use with oligonucleotide target molecule (p. 1750), and teach that with respect to hybridization assays that the no-wash format of many microsphere-based assays, particularly in the final detection step, is considerably faster than assays that require multiple washings (p. 1755). They also teach that the rapid kinetics of micrsphere-based assays that allow shorter incubation times than conventional solid supports (p. 1755).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Wallace *et al.* in view of Gerry *et al.* so as to have provided a microsphere based assay that included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.* so as to have included a flow cytometry step for the detection of hybridization of the extension product, as

taught by Fulton *et al.*. One would have been motivated to utilize such methodology because Fulton *et al.* teach that their system "represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions..." and that their system "...is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis..." offering "excellent sensitivity, precision, speed, and economy (p. 1775)." Thus, one would have been motivated to use a microbead based flow cytometry method as taught by Fulton et al. to detect the alleles present in the sample taught by Wallace *et al.* in view of Gerry *et al.* in order to take advantage of such a system as taught by Fulton *et al.*

9. Claims 20, 23, 25, 26, 27, 28, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* in view of Dubiley *et al.* (Nucleic Acids Research, 1999, Vol. 23, No. 18, page e19).

With regard to claim 20, Chen *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one oligonucleotide primer comprising a hybridization tag that identifies said primer, said primer having a 3' end specific for a single nucleotide polymorphism of interest (p. 550, Col. 1, the primer has a DNA sequence at the 5' end that allows the primer to be captured onto a microbead);

b) combining said at least one primer with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primer to complementary sequences in said single-stranded polynucleotides (p. 556, "SBCE reactions;" Figure 1);

c) extending hybridized primers by primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (p. 556, "SBCE reactions;" Figure 1);

d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a particle that identifies said capture probe (p. 556, "Hybridization of SBCE Reaction Mixture to Microsphere");

e) detecting the hybridization of said extension product to said capture probe using said detectable label (p. 556);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (p. 557).

With regard to claim 23, Chen *et al.* teach that the present invention can be used for the determination of which alleles are present at 4 different SNP (p. 550, Figure 2), and such a method would inherently include the use of a plurality of primers each specific for a different single nucleotide polymorphism.

Chen *et al.* teach a method wherein the 3' end of said primer is immediately adjacent to the location of the single nucleotide polymorphism of interest (p. 556).

With regard to claim 25, the method taught by Chen *et al.* is a single base extension (i.e. the method is called "Single Base Chain Extension" throughout.).

With regard to claim 26, the single base extension is achieved by using only a single type of nucleotide triphosphate, namely all dideoxynucleotide triphosphates (p. 556, SBCE Reactions).

With regard to claims 27 and 28, Chen *et al.* exemplify primer extension can be accomplished using chain terminating nucleotides, namely dideoxynucleoside triphosphates (p. p. 556, SBCE Reactions).

Chen *et al.* do not teach a method wherein said at least one primer comprises a group of at least 2 primers, each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest. With regard to claim 31, Chen *et al.* do not teach or suggest the application of these methodologies to the detection of disease or conditions.

Dubiley *et al.* teach a single nucleotide extension method for the detection of polymorphic alleles which utilized primers that contain different 3'-terminal nucleotide overlapping the variable DNA, and teach a group of at least 2 primers, each primer having a 3' end specific for different alleles of a single nucleotide polymorphism of interest (heading: Materials and Methods; Isothermal single base primer extension assay; Identification of a single base polymorphism with multiprimer assay). In the multiprimer assay, four primers variable at the 3' nucleotide are used to test all four possible bases in the polymorphic site of target DNA (heading: RESULTS; Amplified multibase and multiprimer single-stranded extension). Furthermore, Dubiley *et al.* teach the application of single base extension methodologies to β-Thalassemia diagnosis (heading: RESULTS; β-Thalassemia diagnostics).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have utilized the primers taught by Dubiley *et al.* in the methods taught by Chen *et al.* so as to have provided a method which utilizes a pair of at least two primers, each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest, and further to have utilized the polymorphism detection methods for

the detection of disease related alleles. The use of such primers would have provided an alternate methodology for the detection of single nucleotide polymorphisms using the basic methodology taught by Chen *et al.*, as Dubiley *et al.* teach that the use of primers that end adjacent to or overlap with the polymorphic site have comparable specificity with regard to one another (final page, first full paragraph). The use of the method for the detection of disease alleles would provide the obvious benefit of detecting disease alleles and thus the presence or predisposition to disease.

10. Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen *et al.* in view of Dubiley *et al.* as applied to claims 20, 23, 25, 26, 27, 28, and 31 above, and further in view of Söderlund *et al.* (US 6013431).

The teachings of Chen *et al.* in view of Dubiley *et al.* are applied to claims 29 and 30 as they are applied in the rejection of claims 20, 23, 25, 26, 27, 28, and 31.

While Chen *et al.* utilize labeled chain terminating nucleoside triphosphates, namely dideoxynucleoside triphosphates, Chen *et al.* do not teach a method wherein a plurality of chain-terminating nucleoside triphosphates (p. 555), each comprising a unique label are used, as is recited in claims 29 and 30.

Söderlund *et al.* teach single nucleotide primer extension methods which a method wherein a plurality of chain-terminating nucleoside triphosphates, each comprising a unique label are used for the detection of more than one point mutation occurring at the same site out of one undivided sample (Col. 8, lines 44-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method taught by Chen *et al.* so as to have included

differentially labeled ddNTPs as taught by Söderlund *et al.* within the reaction mixture in order to detect more than one point mutation occurring at the same site of an undivided sample.

11. Claims 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lai *et al.* in view of Fulton *et al.* and Wallace *et al.* (WO93), and further in view of Söderlund *et al.*

The teachings of Lai *et al.* in view of Fulton *et al.* and Wallace *et al.* are applied to claims 29 and 30 as they were previously applied to claims 19, 25, 26, 27, 28, and 31.

While Wallace *et al.* teach methods which utilize labeled chain terminating nucleoside triphosphates, namely dideoxynucleoside triphosphates (p. 10, last line), Wallace *et al.* do not teach a method wherein a plurality of chain-terminating nucleoside triphosphates, each comprising a unique label are used, as is recited in claims 29 and 30.

Söderlund *et al.* teach single nucleotide primer extension methods which a method wherein a plurality of chain-terminating nucleoside triphosphates, each comprising a unique label are used for the detection of more than one point mutation occurring at the same site out of one undivided sample (Col. 8, lines 44-48).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method taught by Lai *et al.* in view of Fulton *et al.* and Wallace *et al.* so as to have included differentially labeled ddNTPs as taught by Söderlund *et al.* within the reaction mixture in order to detect more than one point mutation occurring at the same site of an undivided sample.

12. Claims 20, 23, 25, 26, 27, 28, 29, 30, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al.* in view of Fulton *et al.*

With regard to claim 20, Huang *et al.* teach a method for detecting a single nucleotide polymorphism comprising:

a) providing at least one a group of at least 2 primers in each group, wherein each primer comprises a hybridization tag that identifies said primer, and each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest (Col. 2, lines 50-55; Col. 4, lines 20-25; Col. 17, lines 55-60; Claim 15);

b) combining said at least one primer with a sample containing single stranded polynucleotides under stringent conditions which allow hybridization of said primer to complementary sequences in said single-stranded polynucleotides (Col. 2, lines 45-50);

c) extending hybridized primers by primer extension to produce an extension product, said extension product comprising said hybridization tag and a detectable label (Col. 2, lines 55-57);

d) hybridizing said extension product by said hybridization tag under stringent conditions to a capture probe, said capture probe coupled to a particle that identifies said capture probe (Col. 2, lines 57-59);

e) detecting the hybridization of said extension product to said capture probe using said detectable label (Col. 4, lines 14-16);

f) determining the identity of said single nucleotide polymorphism based on the identity of said particle (Col. 5, lines 43-52).

Huang *et al.* teach that this assay can be multiplexed, thus comprising a plurality of primers specific for a plurality of single nucleotide polymorphisms (Col. 4, lines 20-25). Huang *et al.* teach a method wherein said at least one primer comprises a group of at least 2 primers,

each primer specific for a different allele of a single nucleotide polymorphism of interest (Col. 17, lines 55-60; Claim 15).

With regard to claim 23, Huang *et al.* teach a method further comprising a plurality of said primer groups, each primer group specific for a different single nucleotide polymorphism of interest (Col. 4, lines 20-25).

With regard to claim 25, Huang *et al.* teach a method wherein said prmer extension is a single base primer extension (Col. 8, line 58).

With regard to claim 26, Huang *et al.* teach a method wherein said single base extension is achieved by using only a single type of nucleoside triphosphate, that is dideoxynucleotide triphosphates (Col. 8, line 59).

With regard to claims 27, 28, and 30, Huang *et al.* teach a method wherein said single base extension is achieved by using at least one chain terminating nucleotide triphosphate (Col. 8, line 59).

With regard to claim 29, Huang *et al.* teach that two different fluorescent labels can be used in order to distinguish between two alleles at each polymorphic site examined (Col. 17, lines 55-56).

With regard to claim 31, Huang *et al.* teach that their methods can be employed to detect mutations and identify phenotypes of mutations in clinical diagnostics and clinical studies (Col. 7, lines 25-30).

Huang *et al.* teach that the solid support can be beads (Col. 5, line 46, and claim 7).

Huang *et al.* do not teach a method wherein the detection is by flow cytometry

Fulton *et al.* teach methods of sorting and detecting microspheres which utilize flow cytometry, and in particular teach these methods in conjunction with nucleic acid hybridization methodologies (p. 1753-1755). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Huang *et al.* so as to have included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.* so as to have included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.*, including any necessary modification of the beads taught by Huang et al. necessary for the practice of the flow cytometry methods taught by Fulton et al. One would have been motivated to utilize such methodology because Fulton *et al.* teach that their system "represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions..." and that their system "...is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis..." offering "excellent sensitivity, precision, speed, and economy (p. 1775)." Thus, one would have been motivated to use the flow cytometry based methods taught by Fulton et al. to detect alleles as taught by Huang *et al.* in order to take advantage of such a system as taught by Fulton *et al.*

Response to Remarks

A new ground of rejection is set forth to address the newly added claim. All previously pending rejections are maintained.

Applicant argues at page 8 that the rejection is improper "in that the no suitable suggestion or motivation to combine the references can be found." These arguments are not persuasive.

Regarding the motivation, as discussed in the rejection, Fulton *et al.* specifically teach that the use of microbeads and flow cytometry detection have a wide range of applications. To that end, at page 1750 of the reference, second column, Fulton *et al.* give guidance as to how to apply the use of microbeads to a wide variety of target molecules, including oligonucleotides. At p. 1755, Fulton further expand their discussion of the benefits and wide applicability of their system teaching that "the system has several advantages for analysis of biologically and medically relevant molecules, including speed, economy, and advanced analytical capabilities..." and further specifically suggest the use of the system for capture/sandwich assays, which is precisely the type of system that Lai *et al.* are using. The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation has been cited in the rejection, and this specific motivation is found in the teachings of Fulton *et al.*

At page 8 of the response, application states that "one of skill would have to engage in considerable experimentation in order to reconcile the two teachings" and that there is no reasonable expectation of success if the two teachings were combined. However, these are attorney's arguments which are not supported by any evidence on the record, and which Fulton

et al.'s teachings of the broad applicability of their method seem to contradict. As previously discussed, Fulton *et al.* are very clear in their suggestion that their methods using microspheres and flow cytometry have wide applicability to a variety of different binding assays, specifically mentioning oligonucleotide binding and capture assays. Absolute predictability is not required in order to establish an expectation of success. The MPEP states, "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness (2143.02)." However, in the instant case, no evidence is presented, only the arguments of counsel. The arguments of counsel are not found to be persuasive in the absence of a factual showing. MPEP 716.01(c) makes clear that

> "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

On page 9 of the response, applicants compare the hybridization and capture method exemplified in Fulton *et al.* with that of Lai *et al.* In the instant rejection, Lai *et al.* provides all of the method steps of the claimed invention except the use of flow cytometry. The suggestion to combine the references is a suggestion to modify the method taught by Lai *et al.* so at to take advantage of the "revolutionary" methods taught by Fulton *et al.* Applicant's arguments focused on an exemplified embodiment of Fulton *et al.*, but do not consider the totality of the reference and the specific teachings of Fulton *et al.* as to the wide applicability of their method. MPEP 2123 teaches that "A reference may be relied upon for all that it would have reasonably

suggested to one having ordinary skill the art, including nonpreferred embodiments." In the instant case, Fulton *et al.* exemplify the use of the microbeads with a competition hybridizaiton assay, but suggest its wide applicability to any analyte binding assay, specifically mentioning sandwich and capture assays.

Applicant sets forth further explaination beginning in the second paragraph on page 8, outlining the differences in the microspheres used by Lai et al. versus Fulton et al., and suggesting that in view of the differences, there would have been no valid motivation to combine the references. However, this is not persuasive, because one could have used the microbeads and detection method as taught by Fulton et al. As noted, applicant provides no evidenciary support for the assertion that there is no reasonable expectation of success. The rejection is MAINTAINED.

Applicant's arguments regarding Lai et al. in view of Fulton et al. and further in view of Wallace et al. rely on the previous arguments regarding Lai et al. in view of Fulton et al. These arguments are not persuasive for the reasons previously stated.

Applicant traverses the rejection under the '611 patent in veiw of Gerry et al. and further in view of Fulton et al beginning at page 11 of the response. Applicants argue that Gerry et al. does not provide for the deficinecies of the '611 patent because Gerry et al. does not teach or suggest a capture probe coupled to a microbead wherein detection occurs by flow cytometry (p. 12, 1st full ¶). This is a piecemeal analysis that does not consider the totality of the rejection, and thus it is not persuasive. Applicant further argues that Fulton et al. do not teach how to obtain the desired result when coupled with the disclosures of the '611 patent and Gerry et al. This is not persuasive. As noted in the rejection, Fulton et al. utilize capture probes attached to

microbeads and detection via flow cytometry. Fulton et al. teach methods of sorting and detecting microspheres which utilize flow cytometry, and in particular teach these methods in conjunction with nucleic acid hybridization methodologies (p. 1753-1755). Fulton et al. teach the multiplexed assays which utilize the microspheres are suitable for use with oligonucleotide target molecule (p. 1750), and teach that with respect to hybridization assays that the no-wash format of many microsphere-based assays, particularly in the final detection step, is considerably faster than assays that require multiple washings (p. 1755). They also teach that the rapid kinetics of micrsphere-based assays that allow shorter incubation times than conventional solid supports (p. 1755). Thus, the teachings of Fulton et al. are more than a suggestion to investigate, the specifically exemplify how to use the microbeads in nucleic acid based detection systems. The rejeciotn is maintained.

Applicant traverses the rejeciton under Chen et al. in view of Dubiley et al., stating that there is no motivation to combine the references (see p. 15 of the response). In support of this argument, applicants discuss the differences in methodology between Chen et al. and Dubiley et al. suggesting that the methods are not combinable. However, this is not persuasive. Dubiley et al. are relied upon to provide teaching of a particular type of sets of primers; Chen et al. provide all of the other elements of the claims. Applicant's analysis of the two methods does not take in consideration the totality of the rejection which describes the necessary modification to Chen et al. or the motivation given to modify the method taught by Chen et al. in order to have arrived at the claimed invention. Applicant states that Chen et al. would not have been motivated to utilize the solid phase assays taught by Dubiley et al. as the methods of Chen et al. were more amenable to multiplexing. The examiner has not argued that one would be motivated to use the solid phase

assay of Dubiley et al., but instead to have modified the primers taught by Chen et al. so as to have used those taught by Dubiley et al., and such a modification would have been motivated in order to provide an alternate methodology for the detection of single nucleotide polymorphisms using the basic methodology taught by Chen et al., as Dubiley et al. teach that the use of primers that end adjacent to or overlap with the polymorphic site have comparable specificity with regard to one another (final page, first full paragraph). The use of the method for the detection of disease alleles would provide the obvious benefit of detecting disease alleles and thus the presence or predisposition to disease. The traversal of the rejection under Chen et al. in view of Dubiley et al. and further in veiw of Soderlund et al. and the traversal of the rejeciton of Lai et al. in view of Fulton et al. and Wallace et al. and further in view of Soderlund et al. rely on the previously set forth arguments which have been addressed in both the Final rejection and this Advisory rejection. As the previously set forth arguments were not persuasive, the rejections are maintained.

Applicant's traverse the rejecion under Huang et al. in view of Fulton et al. pointing out differeneces in the two methods and that there would be no motivation to combine the references. The motivation is provided in the rejection. Applicant's arguments that the "sweeping statements" by Fulton et al. do not provide sufficient motivation are not persuasive. As noted previously, Fulton et al. exemplify their method in nucleic acid based assays and very clearly suggest the broad applicability of their methodology. Applicant has provide no evidence that their guidance would not be sufficient.

Thus, all rejections are maintained.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached by calling (571) 272-0745.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as

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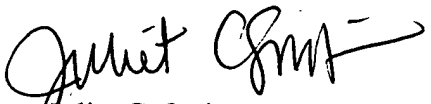

Juliet C. Switzer
Primary Examiner
Art Unit 1634

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